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Dairy fat intake and risk of type 2 diabetes in 3 cohorts of US men and women

Andres V Ardisson Korat,[1,2] Yanping Li,[1] Frank Sacks,[1,3] Bernard Rosner,[4,5] Walter C Willett,[1,2,4] Frank B Hu,[1,2,4] and Qi Sun[1,4]

[1]Department of Nutrition, Harvard TH Chan School of Public Health, Boston, MA, USA; [2]Department of Epidemiology, Harvard TH Chan School of Public Health, Boston, MA, USA; [3]Department of Genetics and Complex Diseases, Harvard TH Chan School of Public Health, Boston, MA, USA; [4]Channing Division of Network Medicine, Brigham and Women's Hospital, Boston, MA, USA; and [5]Department of Biostatistics, Harvard TH Chan School of Public Health, Boston, MA, USA

ABSTRACT

Background: Previous studies have examined dairy products with various fat contents in relation to type 2 diabetes (T2D) risk, although data regarding dairy fat intake per se are sparse.

Objectives: We aimed to evaluate the association between dairy fat intake and risk of T2D in 3 prospective cohorts. We also examined associations for isocalorically replacing dairy fat with other macronutrients.

Methods: We prospectively followed 41,808 men in the Health Professionals Follow-Up Study (HPFS; 1986–2012), 65,929 women in the Nurses' Health Study (NHS; 1984–2012), and 89,565 women in the NHS II (1991–2013). Diet was assessed quadrennially using validated FFQs. Fat intake from dairy products and other relevant sources was expressed as percentage of total energy. Self-reported incident T2D cases were confirmed using validated supplementary questionnaires. Time-dependent Cox proportional hazards regression was used to estimate the HR for dairy fat intake and T2D risk.

Results: During 4,219,457 person-years of follow-up, we documented 16,511 incident T2D cases. Dairy fat was not associated with risk of T2D when compared with calories from carbohydrates (HR for extreme quintiles: 0.98; 95% CI: 0.95, 1.02). Replacing 5% of calories from dairy fat with other sources of animal fat or carbohydrate from refined grains was associated with a 17% (HR: 1.17; 95% CI: 1.13, 1.21) and a 4% (HR: 1.04; 95% CI: 1.00, 1.08) higher risk of T2D, respectively. Conversely, a 5% calorie replacement with carbohydrate from whole grains was associated with a 7% lower risk of T2D (HR: 0.93; 95% CI: 0.88, 0.98).

Conclusions: Dairy fat intake was not associated with T2D risk in these cohort studies of US men and women when compared with calories from carbohydrate. Replacing dairy fat with carbohydrates from whole grains was associated with lower risk of T2D. Replacement with other animal fats or refined carbohydrates was associated with higher risk. *Am J Clin Nutr* 2019;110:1192–1200.

Keywords: dairy fat, type 2 diabetes, carbohydrate from whole grains, carbohydrate from refined grains, animal fat, prospective cohort

Introduction

The prevalence of type 2 diabetes (T2D) has reached an epidemic level. According to estimates from the International Diabetes Federation, 425 million adults worldwide had T2D in 2017 (8.8% of the adult population) (1). The CDC estimated that 23.1 million people were living with diagnosed diabetes in the United

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Address correspondence to QS (e-mail: qisun@hsph.harvard.edu).

Abbreviations used: AHEI, Alternative Healthy Eating Index; CVD, cardiovascular disease; HPFS, Health Professionals Follow-Up Study; IHD, ischemic heart disease; NHS, Nurses' Health Study; TFA, *trans* fatty acid; T2D, type 2 diabetes.

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States in 2015 and the annual age-adjusted incidence of T2D was 6.7 new cases per 1000 US adults (2). Genetic risk factors may determine T2D risk to a certain extent, but they cannot explain the dramatic increases in rates over the last several decades (3, 4).

In the US diet, dairy products are an important food group and in general accounted for 9.4% of total energy intake (5). The current dietary guidelines recommend limiting the intake of high-fat dairy products owing to the concerns regarding high contents of SFAs in dairy fat. Saturated fat intake is a risk factor in the development of ischemic heart disease (IHD), particularly long-chain SFAs (14:0–18:0) when substituting for PUFAs (6). However, evidence regarding associations between dairy fat and T2D risk remains sparse and inconclusive. High-fat dairy products, on average, have not been associated with risk of T2D (7), whereas an inverse association has been observed with intake of low-fat dairy foods (7). However, in these analyses, some important sources of dairy fat such as butter, either consumed directly or as an ingredient of other food products, were usually excluded. Thus, findings from these studies may not directly pertain to dairy fat.

In this analysis, we aimed to evaluate dairy fat intake, derived from various dairy products or as a constituent of other foods, in relation to T2D risk in 3 prospective cohorts of US men and women.

Methods

Study population

We used data from participants in 3 prospective cohorts: the Health Professionals Follow-Up Study (HPFS), the Nurses' Health Study (NHS), and the NHS II. The HPFS started in 1986, with 51,529 male health professionals who were 40–75 y of age at recruitment. The NHS was established in 1976 and recruited 121,701 female nurses aged 30–55 y, and the NHS II was established in 1989 with a recruitment of 116,671 nurses who were 24–44 y of age at enrollment. In all 3 cohorts, questionnaires were administered at baseline to collect information on lifestyle, medical history, and other characteristics, which was updated biennially. The cumulative follow-up rate of the participants in these cohorts was >90%.

In the current analysis, we excluded participants who had diagnoses of diabetes, cancer, or cardiovascular disease (CVD) at baseline (1986 for the HPFS, 1984 for the NHS, and 1991 for the NHS II). In addition, participants were excluded if they left >70 food items blank on the baseline FFQ or reported unusual total energy intakes (i.e., daily energy intake <800 or >4200 kcal/d for men, and <500 or >3500 kcal/d for women). We also excluded participants without baseline information on dairy consumption or T2D diagnosis date, leaving a sample of 41,808 HPFS participants, 65,929 NHS participants, and 89,565 NHS II participants for the present analysis. The study protocol was approved by the institutional review boards of Brigham and Women's Hospital and the Harvard TH Chan School of Public Health. Return of a completed questionnaire was considered as informed consent.

Assessment of diet

An FFQ with 61 items was administered to NHS participants in 1980 to collect information about habitual dietary intake. An expanded questionnaire with 131 items was sent to NHS participants in 1984, 1986, and quadrennially thereafter to update their diet information. In the HPFS, the expanded FFQ has been administered since 1986, and in the NHS II diet has been assessed since 1991, both quadrennially. For each food item in the FFQ, we inquired about consumption frequencies, which ranged from "never or less than once per month" to "6 or more times per day." Dairy fat intake was calculated via multiplying the eating frequency of a food item with a prespecified portion size by the dairy fat content of that food item and then summing the dairy fat intake across all relevant food items. The dairy products considered in the current analysis included whole milk, skim/low-fat milk, sherbet, yogurt, cheese, cream cheese, cream and sour cream, ice cream, frozen yogurt, cottage/ricotta cheese, butter, and other cheese. We also included butter added to food or bread and butter used for sautéing or frying, baking, and cooking at home. Other food items included in the computation included cakes, cookies, pastries, and fried foods, depending on the reported type of fat used for baking or for frying. Intake of other nutrients was calculated using the same algorithm. Nutrient contents of food items were extracted from the Harvard University Food Composition Database. From 1994 in the NHS and HPFS and 1995 in the NHS II, intake of plain yogurt (plain or with NutraSweet) and flavored yogurt (without NutraSweet) was further enquired about. The standard serving size was an 8-oz glass (240 mL) for skim, low-fat milk, and whole milk; 1 cup (8 oz) for yogurt until the 2006 (NHS and HPFS) or 2007 questionnaire (NHS II) or 4–6 oz starting in the 2010 and 2011 questionnaires; 1 tablespoon (20 g) for cream and sour cream; half a cup (122.5 g) for sherbet or frozen yogurt, ice cream, and cottage and ricotta cheese; and 1 oz (30 g) for cream cheese and other cheese. The overall reproducibility and validity of the FFQ have been demonstrated in prior studies using dietary records and biomarkers as reference measurements of diet (8, 9). Regarding dairy products, the deattenuated correlations between FFQ assessments and those by diet records were 0.62 for both high-fat and low-fat dairy products (10).

Ascertainment of study outcome

Incident cases of T2D were identified by self-reports on the follow-up questionnaires and confirmed by a supplementary questionnaire enquiring about symptoms, use of medications, and blood glucose concentrations at diagnosis. This supplementary questionnaire has been validated in previous studies: 97% of questionnaire-confirmed T2D cases were reconfirmed through medical record review by a physician blinded to the participants' exposure status. We used the National Diabetes Data Group criteria to confirm T2D diagnosis before 1998: *1*) manifestation of classic symptoms such as excessive thirst, polyuria, weight loss, and hunger, in conjunction with elevated fasting glucose ≥140 mg/dL (7.8 mmol/L) or nonfasting glucose concentrations ≥200 mg/dL (11.1 mmol/L); *2*) asymptomatic but elevated plasma glucose on 2 separate occasions or abnormal glucose-tolerance test results; or *3*) receiving any hypoglycemic treatment for diabetes. After 1998, a fasting glucose concentration ≥126 mg/dL (7.0 mmol/L) was adopted as per the American Diabetes Association diagnostic criteria.

Assessments of covariates

In the biennial follow-up questionnaires, we enquired about and updated information on body height and weight, cigarette smoking, physical activity, medication use, as well as history of chronic diseases, including diabetes, hypertension, and hypercholesterolemia. Among the NHS and NHS II participants, we ascertained menopausal status, postmenopausal hormone use, and oral contraceptive use in the questionnaires. To quantify diet quality, we calculated a 2010 Alternative Healthy Eating Index (AHEI) score, which summarizes the consumption levels of 10 dietary components that are most predictive of chronic disease risk. Each component was scored from 0 to 10 based on specified thresholds of intake, where 10 indicated the best adherence to the optimal intake, and 0 the poorest adherence. A higher AHEI score reflects higher intakes of fruits, vegetables, whole grains, nuts, long-chain ω-3 (n–3) fatty acids, and PUFAs, and lower intakes of sugar-sweetened beverages, red and processed meats, *trans* fatty acids (TFAs), and sodium (11).

Statistical analyses

Person-years were calculated from the return date of the baseline questionnaire to the date of T2D diagnosis, death, loss to follow-up, or the end of follow-up (NHS: 30 June, 2012; NHS II: 30 June, 2013; HPFS: 31 January, 2012), whichever came first. Dairy fat intake, as percentage of total energy, was categorized into quintiles. In order to represent long-term diet and minimize random within-person variability, we used the cumulative averages of dairy fat intake from the baseline questionnaire to the censoring events (12). Missing covariate data were carried forward from the previous questionnaire cycle. We stopped updating diet when participants developed IHD, stroke, or cancer, or underwent coronary artery bypass surgery, because diagnoses of these outcomes may lead to dietary changes.

We used a time-dependent Cox proportional hazards regression to estimate the HRs for dairy fat intake in relation to T2D risk. All analyses were conducted separately in each cohort, and HRs were combined using an inverse variance–weighted approach. Heterogeneity was assessed using the Cochran's Q test. The basic model was stratified jointly by age and calendar time to control for the impact of these variables as well as their interactions on the associations of interest. In multivariate models, we further controlled for BMI (in kg/m^2), total energy intake, race/ethnicity, smoking, physical activity (metabolic equivalent of task per week), alcohol use, family history of diabetes, and history of hypertension or hypercholesterolemia at baseline. In the NHS and NHS II, we further adjusted for use of oral contraceptives, menopausal status, and postmenopausal hormone use. In the final multivariate model, we further adjusted for AHEI, and intakes of protein, vegetable fat, and animal fat other than dairy fat. For the test for trend, we assigned the median values of each quintile and modelled this variable in the Cox regression analyses. The coefficients from the final model were interpreted as the estimated effect of replacing a specific percentage of energy from carbohydrates with an equivalent percentage of energy from dairy fat, adjusting for dietary quality and other potentially confounding variables.

The associations between risk of T2D and substitutions of other macronutrients for dairy fat were evaluated using a multivariable Cox proportional hazards model where dairy fat intake and other macronutrients were modeled as continuous variables in the same model. We then computed the difference in coefficients from this model to estimate the HRs for replacement of calories from dairy fat with the equivalent calories from other macronutrients, including vegetable fat, PUFAs, other animal fat, total carbohydrate, carbohydrate from whole grains, and carbohydrate from refined grains (13). We ran a series of models to estimate the associations for substitutions of other macronutrients for dairy fat. In addition to adjustment for the same list of covariates considered in the fully adjusted model, we further controlled for *trans* fat intake. Of note, in this model we were able to examine the associations for substituting vegetable fats and other animal fats for dairy fat. We adjusted for the same covariates when we estimated the substitution associations for carbohydrates from different sources, as well as for total PUFAs and plant-based MUFAs, respectively. When we evaluated substitution associations for ω-6 PUFAs and ω-3 PUFAs, we included both variables in the multivariate model. Finally, we further adjusted for ω-3 PUFAs when evaluating linoleic acid (18:2n–6), or ω-6 PUFAs when evaluating α-linolenic acid (18:3n–3).

We tested for potential effect modification of the associations of interest by age ($<$65 y and $\geq$65 y), sex, BMI ($<$25, 25–29.9, and $\geq$30), physical activity (below median, above median), smoking (current, other), baseline hypertension (yes, no), and baseline hypercholesterolemia (yes, no) by including a cross-product term between these categorical variables and dairy fat intake (percentage of energy) in quintiles in the fully adjusted models and evaluated the significance of interaction terms using a log-likelihood ratio test. In sensitivity analyses, we continued updating diets after diagnoses of cancer and CVD outcomes, used the most recent dietary assessments in the analyses, or used the mean of the 2 most recent dietary assessments.

All P values were 2-sided, and 95% CIs were calculated for HRs. Data were analyzed with the Statistical Analysis Systems software package, version 9.4 (SAS Institute, Inc.).

Results

During 4,219,457 person-years of follow-up, we documented 16,511 incident T2D cases in the 3 cohorts. Dairy fat intake was positively associated with white ethnicity, current smoking status, TFA intake, and total calorie intake in all 3 cohorts. In addition, dairy fat consumption was inversely associated with postmenopausal hormone use in women, and with baseline hypertension and hypercholesterolemia, AHEI score, glycemic load, and intakes of alcohol, carbohydrate from whole grains, fruits and vegetables, sugar-sweetened beverages, PUFA:saturated fat ratio, animal fat from other sources, and vegetable fat in the 3 cohorts (**Table 1**, **Supplemental Figure 1**). Correlations differed by cohort for a few variables: dairy fat intake was associated with a higher BMI in the HPFS but with a lower BMI in the NHS II. Dairy fat intake was inversely associated with physical activity in the HPFS and NHS, but no association was observed in the NHS II. Dairy fat was positively correlated with intake of most dairy products and more strongly with high-fat forms, including butter.

TABLE 1 Baseline age-adjusted characteristics of participants in the 3 cohorts according to quintiles of dairy fat (percentage of energy intake)[1]

	HPFS (1986)			NHS (1984)			NHS II (1991)		
Characteristics	Q1 ($n = 8361$)	Q3 ($n = 8362$)	Q5 ($n = 8361$)	Q1 ($n = 13,185$)	Q3 ($n = 13,186$)	Q5 ($n = 13,186$)	Q1 ($n = 17,913$)	Q3 ($n = 17,913$)	Q5 ($n = 17,913$)
Dairy fat, % of energy	2.8 ± 0.8	5.9 ± 0.4	11.4 ± 3.0	3.5 ± 0.7	6.0 ± 0.3	10.5 ± 2.3	3.5 ± 0.9	6.5 ± 0.4	11.5 ± 2.6
Age, y	54.0 ± 9.4	52.6 ± 9.5	53.4 ± 9.7	50.7 ± 7.0	50.1 ± 7.1	50.1 ± 7.2	36.9 ± 4.6	36.0 ± 4.7	35.4 ± 4.7
Physical activity, MET-h/wk	23.0 ± 32.7	21.5 ± 28.7	19.6 ± 27.8	14.7 ± 20.4	14.2 ± 20.4	13.2 ± 21.3	20.8 ± 28.7	20.9 ± 27.0	20.7 ± 27.2
BMI, kg/m^2	24.5 ± 4.9	24.9 ± 4.9	25.2 ± 5.0	24.5 ± 4.4	25.0 ± 4.6	24.9 ± 4.8	24.6 ± 5.4	24.7 ± 5.3	24.4 ± 5.2
BMI 25 to <30	39.7	44.8	45.6	24.0	25.5	24.4	19.9	21.2	19.8
BMI ≥30	6.2	7.7	9.2	9.9	12.1	12.3	14.0	13.5	12.2
Race, white	91.3	95.8	96.6	95.1	98.6	99.0	92.3	97.5	97.8
Current smoker	9.0	8.3	12.1	23.6	21.5	29.4	13.8	11.1	13.4
Hypertension	22.3	19.0	17.2	21.8	20.1	18.8	6.7	6.0	5.4
High cholesterol	15.3	9.5	6.6	11.1	7.0	5.9	17.3	13.9	12.0
Family history of diabetes	23.4	23.8	24.1	28.6	28.7	27.5	35.8	34.8	33.2
Postmenopausal	NA	NA	NA	46.2	45.1	45.4	4.0	2.8	2.6
Current menopausal hormone use[2]	NA	NA	NA	11.8	11.2	9.9	3.4	2.4	2.1
Current oral contraceptive	NA	NA	NA	NA	NA	NA	10.8	11.3	10.7
Total energy, kcal/d	1910 ± 617	2021 ± 606	2050 ± 658	1676 ± 429	1769 ± 428	1792 ± 467	1734 ± 565	1822 ± 541	1784 ± 556
AHEI	50.0 ± 11.6	46.7 ± 10.3	43.4 ± 10.0	48.0 ± 9.7	46.1 ± 8.6	43.2 ± 8.5	45.4 ± 11.5	43.8 ± 10.2	42.5 ± 9.7
Dairy intake, servings/d	0.8 ± 0.6	1.9 ± 1.0	3.2 ± 1.7	1.3 ± 0.7	2.1 ± 0.8	2.7 ± 1.1	1.0 ± 0.6	2.2 ± 1.0	3.6 ± 1.7
Alcohol, g/d	13.9 ± 18.7	11.2 ± 14.6	9.5 ± 13.3	6.8 ± 10.9	5.6 ± 8.6	5.8 ± 8.9	3.2 ± 6.9	3.1 ± 5.8	3.1 ± 5.9
Glycemic load	131 ± 32	125 ± 24	116 ± 23	107 ± 20	103 ± 16	96 ± 17	130 ± 26	121 ± 19	113 ± 19
Carbohydrate from whole grains, % of total energy	3.8 ± 4.0	3.1 ± 2.7	2.4 ± 2.2	3.4 ± 2.5	3.2 ± 2.0	2.5 ± 1.8	3.3 ± 3.1	3.1 ± 2.4	2.7 ± 2.1
Vegetable fat, % of total energy	13.8 ± 5.3	13.8 ± 4.3	12.5 ± 4.1	14.9 ± 3.8	14.5 ± 3.3	13.7 ± 3.5	14.7 ± 4.6	14.2 ± 3.8	13.2 ± 3.9
Animal fat from other sources, % of total energy	12.4 ± 5.6	12.2 ± 4.6	11.6 ± 4.4	11.5 ± 3.9	10.9 ± 3.2	10.6 ± 3.3	11.7 ± 4.7	10.6 ± 3.8	9.4 ± 3.8
Polyunsaturated: saturated fat ratio	0.74 ± 0.3	0.56 ± 0.2	0.42 ± 0.1	0.68 ± 0.16	0.57 ± 0.11	0.45 ± 0.10	0.62 ± 0.20	0.51 ± 0.13	0.40 ± 0.11
trans Fat, % of total energy	1.1 ± 0.6	1.3 ± 0.5	1.4 ± 0.5	1.6 ± 0.5	1.6 ± 0.5	1.6 ± 0.4	1.6 ± 0.7	1.6 ± 0.6	1.6 ± 0.6
Fruit and vegetables, servings/d	6.0 ± 3.3	5.4 ± 2.7	4.7 ± 2.4	5.5 ± 2.2	5.3 ± 1.9	4.7 ± 1.9	5.3 ± 3.3	5.2 ± 2.8	4.6 ± 2.6
Red and processed meat intake, servings/d	1.0 ± 0.9	1.2 ± 0.8	1.2 ± 0.8	0.93 ± 0.56	0.95 ± 0.50	0.98 ± 0.54	1.2 ± 0.8	1.2 ± 0.7	1.0 ± 0.7
Nut intake, servings/d	0.5 ± 0.7	0.5 ± 0.6	0.4 ± 0.6	0.1 ± 0.2	0.1 ± 0.2	0.1 ± 0.2	0.1 ± 0.3	0.1 ± 0.2	0.1 ± 0.2
SSB intake, servings/d	0.4 ± 0.7	0.4 ± 0.6	0.3 ± 0.6	1.1 ± 0.9	1.1 ± 0.8	1.0 ± 0.8	0.7 ± 1.2	0.4 ± 0.8	0.3 ± 0.6

[1] Values are means ± SDs or percentages. Data were age-standardized except for age. AHEI, Alternative Healthy Eating Index; HPFS, Health Professionals Follow-Up Study; MET, metabolic equivalent; NA, not available; NHS, Nurses' Health Study; Q, quintile; SSB, sugar-sweetened beverage.

[2] Current menopausal hormone users among postmenopausal women.

Spearman rank correlation coefficients with dairy fat intake were 0.51–0.61 for total dairy, 0.68–0.73 for high-fat dairy products, 0.13–0.22 for low-fat dairy products, and 0.33–0.45 for butter (**Supplemental Table 1**).

In the age-adjusted model, a 5% increase in energy from dairy fat was not associated with T2D risk (pooled HR: 1.00; 95% CI: 0.97, 1.03), as shown in **Table 2**. Further adjustment for lifestyle, demographic, and dietary variables attenuated the significant inverse association observed in the NHS II, and the pooled HR (95% CI) was 0.98 (0.95, 1.02) comparing 5% calories from dairy fat with the equivalent calories from carbohydrates. Stratified analysis did not show any significant interactions by age, sex, BMI, smoking status, physical activity, baseline hypertension, or baseline hypercholesterolemia (all P values > 0.05) (**Table 3**).

In isocaloric substitution models, the replacement of 5% of calories from dairy fat with the equivalent energy from other sources of animal fat was associated with a 17% higher T2D risk (HR: 1.17; 95% CI: 1.13, 1.21), and replacement by carbohydrates from refined grains was associated with a 4% higher T2D risk (HR: 1.04; 95% CI: 1.00, 1.08) (**Figure 1**). Conversely, a 5% calorie substitution by carbohydrates from whole grains was significantly associated with a 7% lower risk of T2D (HR: 0.93; 95% CI: 0.88, 0.98) and a 0.3% calorie substitution of α-linolenic acid was significantly associated with a 5% lower risk of T2D (HR: 0.95; 95% CI: 0.90, 0.995). We did not observe a significant association when replacing 5% of calories from dairy fat with the same percentage of energy intake from vegetable fat, PUFAs, or total carbohydrates

TABLE 2 HRs (95% CIs) of type 2 diabetes risk according to quintiles of dairy fat consumption in the HPFS, NHS, and NHS II[1]

	Quintiles of dairy fat consumption						
	1	2	3	4	5	*P*-trend[2]	HR (95% CI) for 5% of energy
HPFS							
Daily intake,[3] % of energy	2.9	4.2	5.3	6.6	9.2		
Cases/person-years	648/167,284	700/167,228	700/167,126	729/167,151	788/166,893		
Age-adjusted[4]	1.00	1.11 (0.99, 1.23)	1.11 (1.00, 1.24)	1.16 (1.04, 1.29)	1.24 (1.12, 1.37)	<0.0001	1.12 (1.05, 1.19)
Adjusted for lifestyle variables[5]	1.00	1.07 (0.96, 1.19)	1.04 (0.93, 1.16)	1.05 (0.94, 1.17)	1.10 (0.99, 1.22)	0.14	1.04 (0.98, 1.11)
Adjusted for dietary factors[6]	1.00	1.05 (0.95, 1.17)	1.03 (0.92, 1.15)	1.04 (0.93, 1.16)	1.08 (0.97, 1.21)	0.25	1.03 (0.97, 1.10)
NHS							
Daily intake,[3] % of energy	3.7	5.0	6.0	7.3	9.7		
Cases/person-years	1356/315,221	1427/315,007	1352/315,121	1446/315,109	1421/315,149		
Age-adjusted[4]	1.00	1.06 (0.98, 1.14)	1.01 (0.93, 1.09)	1.08 (1.00, 1.16)	1.05 (0.98, 1.14)	0.17	1.03 (0.99, 1.08)
Adjusted for lifestyle variables[5]	1.00	1.01 (0.94, 1.09)	0.94 (0.87, 1.01)	0.98 (0.91, 1.06)	0.96 (0.89, 1.04)	0.29	0.98 (0.93, 1.03)
Adjusted for dietary factors[6]	1.00	1.02 (0.95, 1.10)	0.94 (0.87, 1.02)	1.00 (0.92, 1.08)	0.99 (0.91, 1.06)	0.63	1.00 (0.95, 1.05)
NHS II							
Daily intake,[3] % of energy	3.5	4.8	5.9	7.2	9.5		
Cases/person-years	1377/361,225	1225/362,152	1119/362,211	1129/361,565	1014/361,016		
Age-adjusted[4]	1.00	0.93 (0.86, 1.00)	0.93 (0.86, 1.00)	0.89 (0.82, 0.97)	0.82 (0.75, 0.89)	<0.0001	0.87 (0.83, 0.92)
Adjusted for lifestyle variables[5]	1.00	0.93 (0.86, 1.00)	0.96 (0.89, 1.04)	0.95 (0.88, 1.03)	0.89 (0.82, 0.97)	0.02	0.93 (0.88, 0.98)
Adjusted for dietary factors[6]	1.00	0.93 (0.86, 1.01)	0.97 (0.89, 1.05)	0.96 (0.88, 1.04)	0.91 (0.83, 0.99)	0.06	0.93 (0.88, 0.99)
Pooled analysis							
Age-adjusted[4]	1.00	1.01 (0.97, 1.06)[7]	1.00 (0.95, 1.04)[7]	1.02 (0.97, 1.07)[7]	1.00 (0.95, 1.05)[7]	0.98	1.00 (0.97, 1.03)[7]
Adjusted for lifestyle variables[5]	1.00	0.99 (0.94, 1.04)	0.97 (0.92, 1.01)	0.98 (0.94, 1.03)	0.96 (0.92, 1.01)[7]	0.19	0.98 (0.95, 1.01)[7]
Adjusted for dietary factors[6]	1.00	0.99 (0.94, 1.04)	0.97 (0.92, 1.02)	0.99 (0.94, 1.04)	0.97 (0.93, 1.02)[7]	0.38	0.98 (0.95, 1.02)

[1] HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study.

[2] *P*-trend was calculated by assigning median values to each quintile and was treated as a continuous variable.

[3] Median values.

[4] Cox proportional hazards model stratified jointly by age and calendar time.

[5] Model was further adjusted for BMI (in kg/m^2) (<23, 23–23.9, 24–24.9, 25–26.9, 27–28.9, 29–30.9, 31–32.9, 33–34.9, >35), total energy intake (quintiles), race, smoking, physical activity (quintiles), alcohol consumption (quartiles), menopausal status and menopausal hormone use (NHS and NHS II participants only), oral contraceptive use (NHS II participants only), baseline hypertension, baseline hypercholesterolemia, and family history of diabetes.

[6] Model included the same set of lifestyle variables adjusted in the previous model and was further adjusted for Alternative Healthy Eating Index and dietary intakes of protein, vegetable fat, and animal fat without dairy fat.

[7] *P* for heterogeneity <0.05.

($P > 0.05$). Replacing dairy fat with the same energy intake from ω-6 fatty acids, linoleic acid, MUFAs from plant sources, or total ω-3 fatty acids was also not associated with T2D risk ($P > 0.05$).

In sensitivity analyses, we used different methods to update diet and examined the associations between dairy fat and T2D risk (**Supplemental Table 2**), as well as the associations for substitution effects (**Supplemental Table 3**A, B). Overall, the associations between dairy fat intake and T2D risk did not change substantially in these sensitivity analyses, except that the association for replacement of dairy fat with refined grains was attenuated when using the most recent (HR: 1.00; 95% CI: 0.97, 1.03) or the means of the 2 immediately preceding diet assessments (HR: 1.01; 95% CI: 0.98, 1.04).

Discussion

In the current analysis of 3 prospective cohorts of US men and women, intake of dairy fat was not significantly associated with T2D risk compared with energy from carbohydrates. However, replacing calories from dairy fat with the equivalent calories from animal fat from other sources or carbohydrates from refined grains was significantly associated with a higher T2D risk, whereas replacing dairy fat with carbohydrates from whole grains was significantly associated with a lower T2D risk. These modest associations largely persisted among individuals with various T2D risk profiles or when different analytic approaches were used.

To our knowledge, this is the first study that prospectively examined the association between dairy fat intake and risk of

TABLE 3 HRs (95% CIs) of type 2 diabetes risk according to dairy fat intake stratified by age, sex, BMI, physical activities, smoking status, hypertension, and high cholesterol based on pooled data from the HPFS, NHS, and NHS II[1]

	Quintiles of dairy fat consumption					HR (95% CI) for 5% of energy	*P*-interaction[2]
	1	2	3	4	5		
Age							0.31
<65 y (11,452 cases)	1.00	0.96 (0.90, 1.01)	0.96 (0.90, 1.02)	0.94 (0.89, 1.00)	0.93 (0.88, 0.99)	0.96 (0.92, 0.99)	
≥65 y (5059 cases)	1.00	1.03 (0.95, 1.13)	0.95 (0.87, 1.04)	1.03 (0.94, 1.13)	0.99 (0.90, 1.08)	1.00 (0.94, 1.05)	
Sex							0.37
Male (3565 cases)	1.00	1.05 (0.94, 1.17)	1.03 (0.92, 1.15)	1.03 (0.92, 1.15)	1.07 (0.95, 1.19)	1.03 (0.96, 1.09)	
Female (12,946 cases)	1.00	0.96 (0.91, 1.01)	0.94 (0.88, 0.99)	0.95 (0.90, 1.00)	0.92 (0.87, 0.97)	0.95 (0.91, 0.98)	
BMI, kg/m^2							0.12
<25 (2395 cases)	1.00	0.97 (0.85, 1.09)	0.95 (0.84, 1.08)	1.00 (0.88, 1.13)	0.89 (0.78, 1.01)	0.93 (0.85, 1.00)	
25–29.9 (4806 cases)	1.00	0.98 (0.90, 1.07)	0.95 (0.86, 1.03)	0.97 (0.88, 1.06)	1.04 (0.95, 1.14)	1.03 (0.97, 1.09)	
≥30 (9310 cases)	1.00	1.00 (0.94, 1.07)	0.99 (0.93, 1.06)	1.00 (0.94, 1.07)	0.98 (0.91, 1.05)	0.99 (0.94, 1.03)	
Physical activity							0.23
< Median level (9713 cases)	1.00	1.00 (0.94, 1.07)	0.98 (0.92, 1.04)	0.96 (0.90, 1.03)	0.97 (0.91, 1.04)	0.97 (0.93, 1.01)	
≥ Median level (5393 cases)	1.00	0.96 (0.88, 1.04)	0.93 (0.85, 1.01)	0.96 (0.88, 1.04)	0.90 (0.82, 0.98)	0.96 (0.90, 1.01)	
Smoking status							0.23
Current (1612 cases)	1.00	1.07 (0.91, 1.25)	0.92 (0.79, 1.09)	0.93 (0.79, 1.10)	0.83 (0.71, 0.97)	0.88 (0.80, 0.96)	
Other (14,899 cases)	1.00	0.97 (0.92, 1.02)	0.95 (0.91, 1.00)	0.97 (0.92, 1.02)	0.96 (0.91, 1.01)	0.98 (0.94, 1.01)	
Hypertension							0.12
No (9469 cases)	1.00	0.94 (0.88, 1.00)	0.94 (0.88, 1.01)	0.96 (0.90, 1.02)	0.94 (0.88, 1.00)	0.98 (0.94, 1.02)	
Yes (7042 cases)	1.00	1.04 (0.97, 1.12)	0.97 (0.90, 1.05)	0.97 (0.90, 1.05)	0.96 (0.90, 1.04)	0.95 (0.90, 1.00)	
High cholesterol							0.11
No (9836 cases)	1.00	0.99 (0.93, 1.05)	0.99 (0.93, 1.06)	1.00 (0.94, 1.07)	0.98 (0.91, 1.04)	0.98 (0.94, 1.02)	
Yes (6675 cases)	1.00	0.97 (0.90, 1.04)	0.91 (0.84, 0.98)	0.92 (0.85, 0.99)	0.90 (0.83, 0.97)	0.93 (0.88, 0.98)	

[1]HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study.

[2]Interaction *P* values were calculated using a categorical dairy fat variable (quintiles) by comparing the models with and without interaction terms using a log-likelihood ratio test. A Cox proportional hazards model was stratified jointly by age and calendar time and adjusted for BMI (<23, 23–23.9, 24–24.9, 25–26.9, 27–28.9, 29–30.9, 31–32.9, 33–34.9, >35), total energy intake (quintiles), race, smoking, physical activity (quintiles), alcohol consumption (quartiles), menopausal status and menopausal hormone use, oral contraceptive use, baseline hypertension, baseline hypercholesterolemia, family history of diabetes, Alternative Healthy Eating Index, and dietary intakes of protein, vegetable fat, and animal fat without dairy fat.

T2D, in comparison with other macronutrient sources. A recent meta-analysis of 22 cohorts reported a weak inverse association between T2D and total dairy intake, which may be largely driven by low-fat dairy product intake, with a null association observed for high-fat dairy products (7). In addition, another meta-analysis of 4 cohort studies reported a weak inverse association between butter intake and T2D risk (14). It is difficult to extrapolate these findings to estimate the health effects of dairy fat intake, because dairy products may be used as ingredients in many food products, and thus associations with specific high-fat dairy products may not reflect the effects of total dairy fat intake. Moreover, other nutrients in dairy products, such as calcium and vitamin D, may also determine the associations of dairy products with T2D (15). Lastly, the comparison macronutrients were not specified, because the exposures of interest were dairy products rather than dairy fat intake in the studies included in the meta-analyses.

In the current analysis, replacing dairy fat with different carbohydrate sources showed divergent associations. The finding that replacing dairy fat with refined carbohydrates was associated with a higher risk of T2D deserves discussion. Refined carbohydrate intake may lead to elevated risk of developing T2D through several pathways such as increased insulin resistance and the loss of β-cell function stemming from exhaustion or cell toxicity or through elevated free fatty acid production (16). Interestingly, randomized controlled trials showed that replacing SFAs with refined carbohydrates resulted in similar plasma insulin and glucose concentrations (17), suggesting that both macronutrients are potentially equally detrimental to glucose metabolism (18, 19). Additionally, although dairy fat is high in saturated fat, it also contains other fatty acids with various health effects (20). For example, the composition of dairy fat is 25–30% MUFAs, 2–3% PUFAs, 2% TFAs, and ~0.5% conjugated linoleic acid from ruminant fermentation (21). Thus, replacing dairy fat with refined carbohydrates may not be entirely equivalent to replacing SFAs with other sources of energy. In contrast, replacing dairy fat with carbohydrates from whole grains was associated with a lower T2D risk. In controlled feeding trials, intake of whole grains improves glucose tolerance and peripheral insulin sensitivity compared with intake of refined grains (22–24). These health effects may be explained by the physical properties of the grains (composition, particle size, and type of fiber) that enhance satiety and slow absorption of simple carbohydrates (25). In addition, beneficial phytochemicals in whole grains, such as lignans and alkylresorcinols (26), as well as the production of SCFAs in the colon (27), may also underlie the health benefits of consuming whole grains.

Replacing dairy fat with other fats may help to meet the dietary guidelines that recommend reducing SFA intake to <10% of total

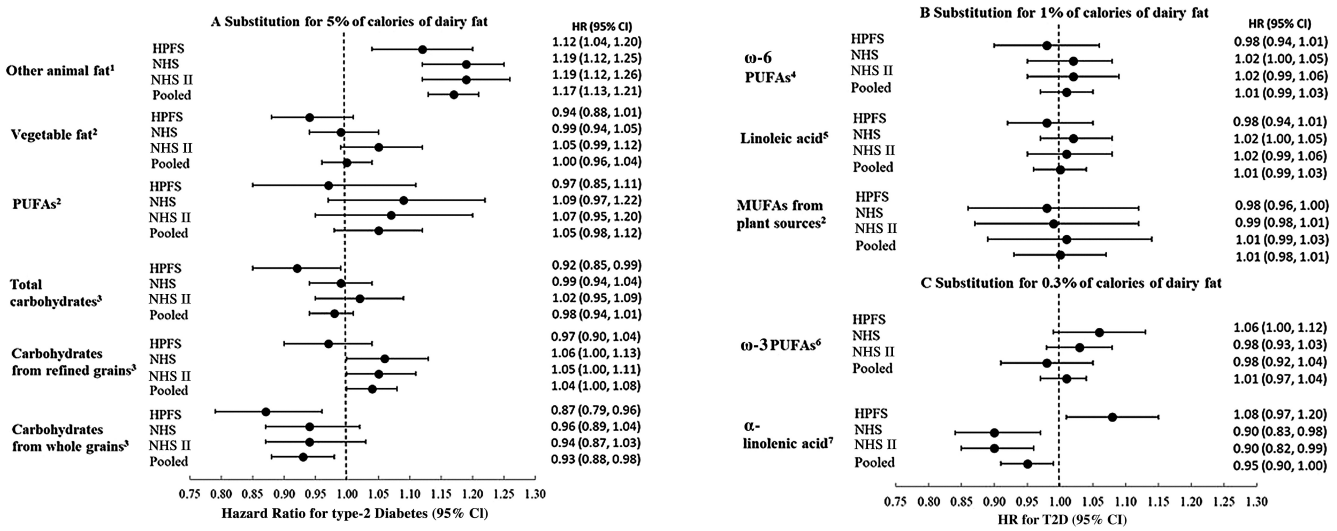

FIGURE 1 HRs (95% CIs) of T2D associated with isocaloric substitutions of selected nutrients for 5% calories of dairy fat (A), 1% calories of dairy fat (B), and 0.3% calories of dairy fat (C) in the HPFS, NHS, and NHS II. A Cox proportional hazards model was stratified jointly by age and calendar time and adjusted for BMI (in kg/m^2) (<23, 23–23.9, 24–24.9, 25–26.9, 27–28.9, 29–30.9, 31–32.9, 33–34.9, >35), total energy intake (quintiles), race, smoking, physical activity (quintiles), alcohol consumption (quartiles), menopausal status and menopausal hormone use (NHS and NHS II participants only), oral contraceptive use (NHS II participants only), baseline hypertension, baseline hypercholesterolemia, family history of diabetes, and dietary intake of *trans* fat, and also for the following covariates: *1*) in the model for the substitution of other animal fat, we further controlled for intake of vegetable fat; *2*) in the models for the substitution of vegetable fat, MUFAs from plant sources, and PUFAs, we further controlled for intake of other animal fat; *3*) in the models for the substitution of total carbohydrate, carbohydrate from refined grains, and carbohydrate from whole grains, we further controlled for intakes of vegetable fat and other animal fat; *4*) in the model for the substitution of ω-6 PUFAs, we further controlled for intakes of other animal fat and ω-3 PUFAs; *5*) in the model for the substitution of linoleic acid, we further controlled for intakes of other animal fat, ω-3 PUFAs, and arachidonic acid; *6*) in the model for the substitution of ω-3 PUFAs, we further controlled for intakes of other animal fat and ω-6 PUFAs; and *7*) in the model for the substitution of α-linolenic acid, we further controlled for intakes of other animal fat, ω-6 PUFAs, and EPA and DHA. HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study; T2D, type 2 diabetes.

energy. In the current analysis, substituting 5% of calories from dairy fat with the equivalent calories from other animal fats was positively associated with T2D risk, which was expected given the positive association between animal fat intake and T2D risk (28, 29). The SFA contents of other animal fats (e.g., lard or tallow) are in the range of 40–50% (30), which is lower than the SFA content in dairy fat. Moreover, the SFA composition differs between dairy fat and other animal fat. Other animal fat sources contain almost exclusively 14:0–18:0, which are also present in dairy fat in comparable amounts. In contrast, ~10% of SFAs in dairy fat are short- and medium-chain SFAs (4:0–10:0) which are absent in other animal fats (21). These SFAs may have different health effects. For example, positive associations for 12:0–18:0 and null associations for 4:0–10:0 have been demonstrated with CVD outcomes (6). In a feeding trial, intake of 6:0–10:0 together with dairy proteins for 12 wk did not increase concentrations of inflammatory markers (31). However, it is unclear if the effects are due to fatty acid or dairy protein intake. Clearly, more evidence is needed to further substantiate the associations between individual SFAs with different chain lengths and metabolic health outcomes.

The isocaloric replacement of dairy fat with MUFAs from different food sources was not associated with T2D risk. The primary dietary MUFA is oleic acid (18:1), which is also the primary MUFA in milk fat, accounting for 25% of total dairy fat. It is likely that replacing the same MUFA between dairy fat and other sources may not lead to significant change in diabetes risk. Surprisingly, replacing calories from dairy fat with calories from PUFAs was not significantly associated with T2D risk in the current analysis, except for a significant T2D risk reduction when replacing dairy fat calories with calories from α-linolenic acid. This finding was unexpected given the reported inverse associations between self-reported PUFA intake (28, 29), as well as biomarkers of ω-6 fatty acids, and T2D risk (32). In addition, dairy fat only contains 2–3% PUFAs and therefore is not a significant source of total PUFA intake. Nonetheless, more studies are warranted to further elucidate these associations.

The validity of dietary intake assessment is critical in nutritional epidemiology, and biomarkers can complement the assessment of intake by questionnaires. Our findings stand in contrast with the inverse associations reported in a pooled analysis of 16 cohorts for blood concentrations of fatty acids found in dairy fat, such as pentadecanoic (15:0), heptadecanoic (17:0), and *trans*-palmitoleic acids (*trans* 16:1n–7), and T2D risk (33). These fatty acids have been considered biomarkers of dairy intake because their concentrations in plasma and erythrocytes are positively associated with dairy intake in both observational studies (9, 34) and feeding trials (35, 36). However, the correlations between these fatty acids and dairy fat intake were in general weak-to-modest. For example, in the NHS and HPFS, we observed correlation coefficients of 0.29 for pentadecanoic acid, 0.21 for heptadecanoic acid, and 0.22 for *trans*-palmitoleic acid when dairy fat was assessed using FFQs (37). Moreover, dairy fat is not the only source of these fatty acids. Recent evidence has suggested that fish also contains odd-chain fatty acids (38). Furthermore, plasma concentrations of pentadecanoic acid and heptadecanoic acid have been detected

in a study among vegan women, suggesting that these fatty acids can be derived from other potential sources than dairy or animal products (39). Gut microbiota processing of soluble fiber (40) and endogenous elongation (41) may explain the production of heptadecanoic acid from a vegan diet. Thus, more sensitive and specific markers of dairy fat are needed to facilitate the examination of associations between dairy fat intake and cardiometabolic diseases. Finally, it is difficult to estimate isocaloric substitution effects using biomarkers of dairy fat because it is difficult to use the biomarkers to quantify the actual intake.

Our study has some limitations to acknowledge. Our parti cipants are exclusively health professionals and 95% of them are of European ancestry. Although the participants' educational attainment, interests in health, and relatively homogeneous socioeconomic status may aid in the collection of high-quality data through self-administered questionnaires and help alleviate confounding by socioeconomic status, such homogeneity may also limit the generalizability of study findings to other populations with different characteristics. T2D cases were identified by self-reports in biannual questionnaires. However, they were confirmed with the use of a validated supplementary questionnaire. In addition, the misclassification of diabetes diagnosis is largely independent of the dairy fat assessments in this prospective study. There is inevitable measurement error in the intake assessment of dairy fat and other nutrients. The FFQ has been extensively validated against dietary records, and the assessments of dairy products have been demonstrated to be quite accurate. In addition, we used repeated measurements to reduce random measurement errors and represent long-term diets. Given the prospective nature of the current analysis, such measurement errors were independent of disease ascertainment and therefore are more likely to attenuate the true association toward the null. Finally, owing to the observational nature of the current analysis, we cannot exclude the possibility that residual or unmeasured confounding accounts for some of the associations, although we controlled an array of established and potential risk factors for T2D.

To conclude, in this prospective investigation among US men and women, intake of dairy fat was not associated with T2D risk, compared with calories from carbohydrates. Replacing dairy fat with other animal fats or carbohydrates from refined grains is associated with a higher T2D risk, whereas replacement by calories from whole grains is associated with a lower risk. These results add further evidence suggesting that the source and type of macronutrients are important for the prevention of T2D.

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